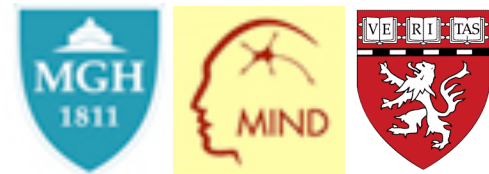


SWAN: Semantic Web Applications in Neuromedicine

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Paolo Ciccarese
Marco Ocana
Harvard / MGH

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IBM Cambridge



What is SWAN?

Semantic Web Applications in Neuromedicine

SWAN is a project to create

- A common digital framework for shared knowledge annotation and organization of scientific discourse
- A robust community process for sharing knowledge via the framework
- A scalable environment for use of Semantic Web in real biomedical applications by bench scientists

What is SWAN Not?

SWAN isn't a project to create

- A model of biology
- A model of the internal structure of discourse
- A “correct view” of scientific theory

Ontology of Discourse

SWAN is about the coarse-grained semantics of scientific discourse, specifically:

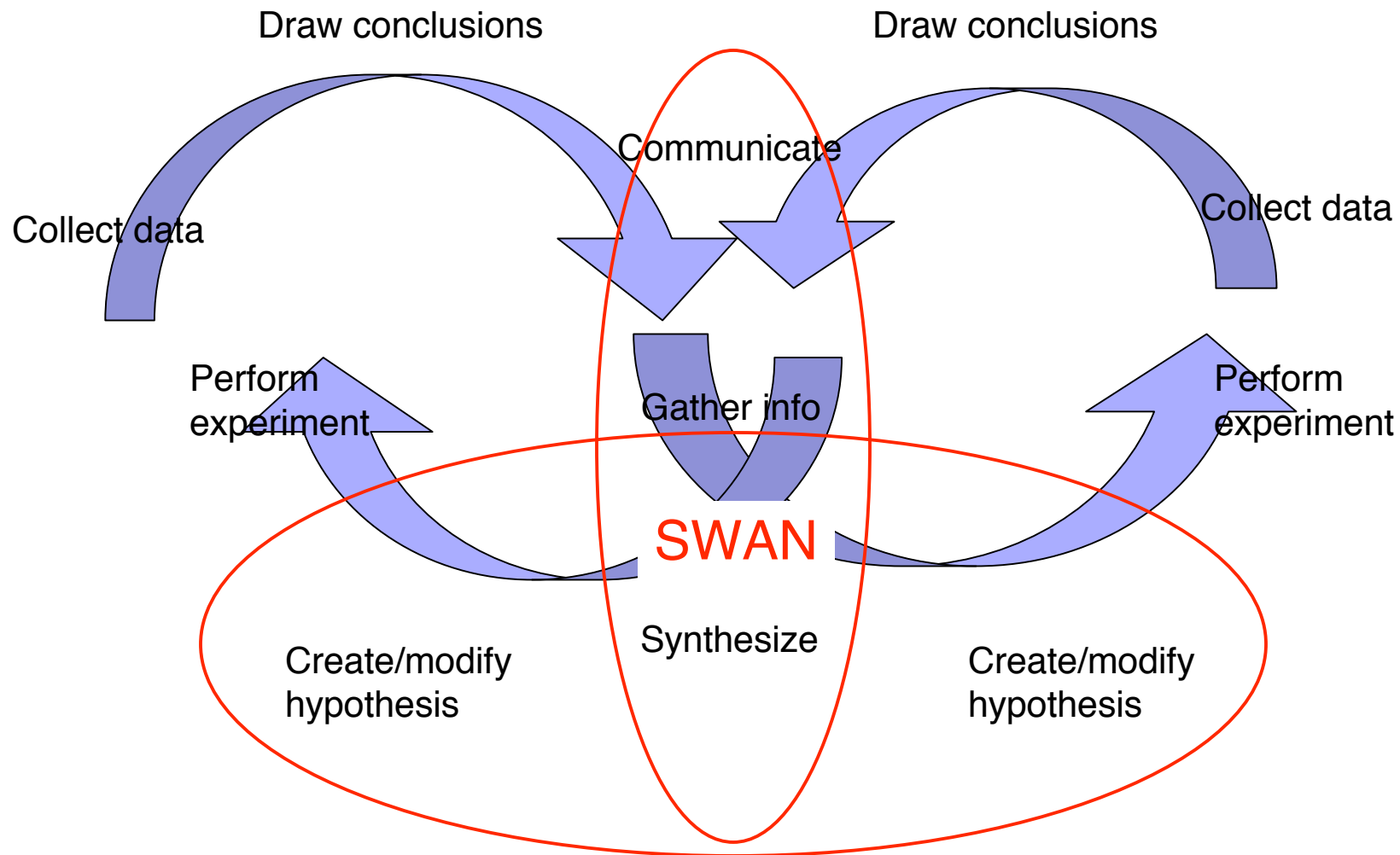
what assertions are made in publications;

what is the evidence for these assertions;

how assertions from one publication relate to another;

how the assertions connect to concepts in other ontologies.

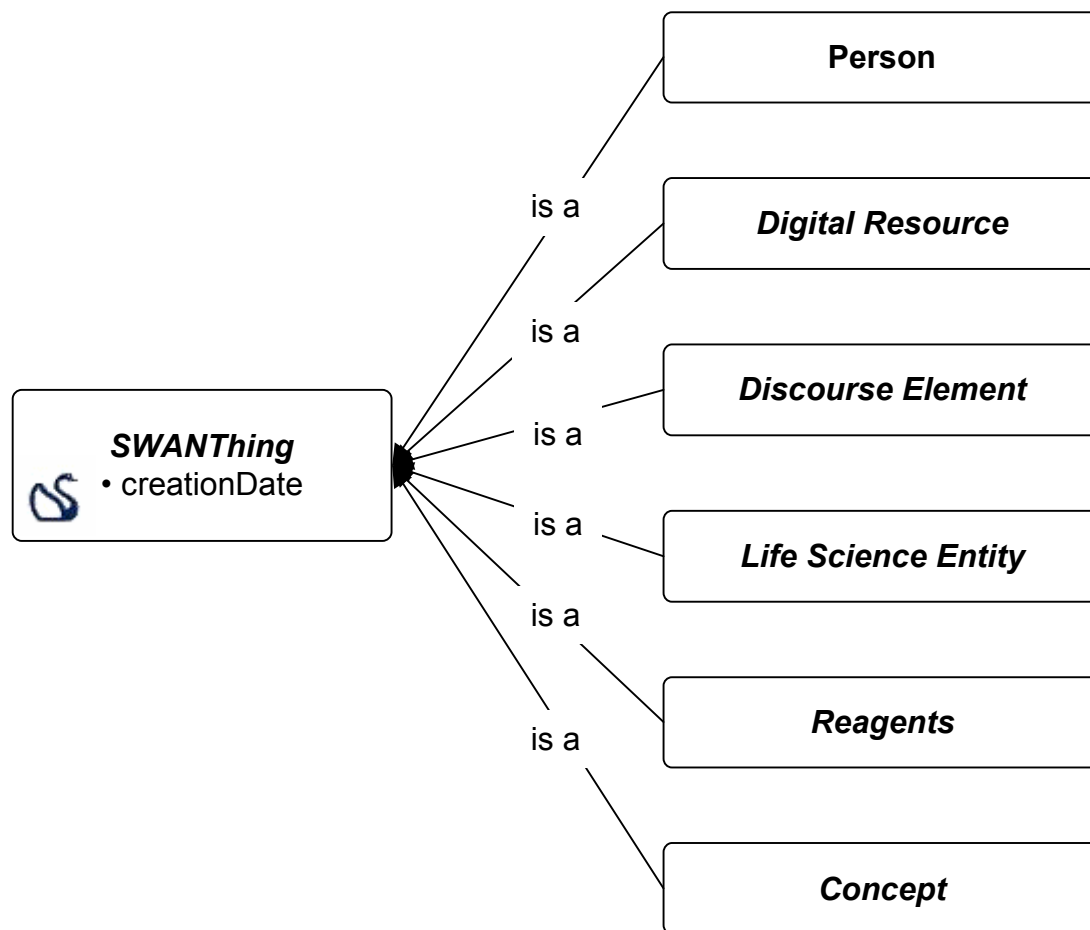
The Knowledge Ecosystem: Interlocking Cycles of Research



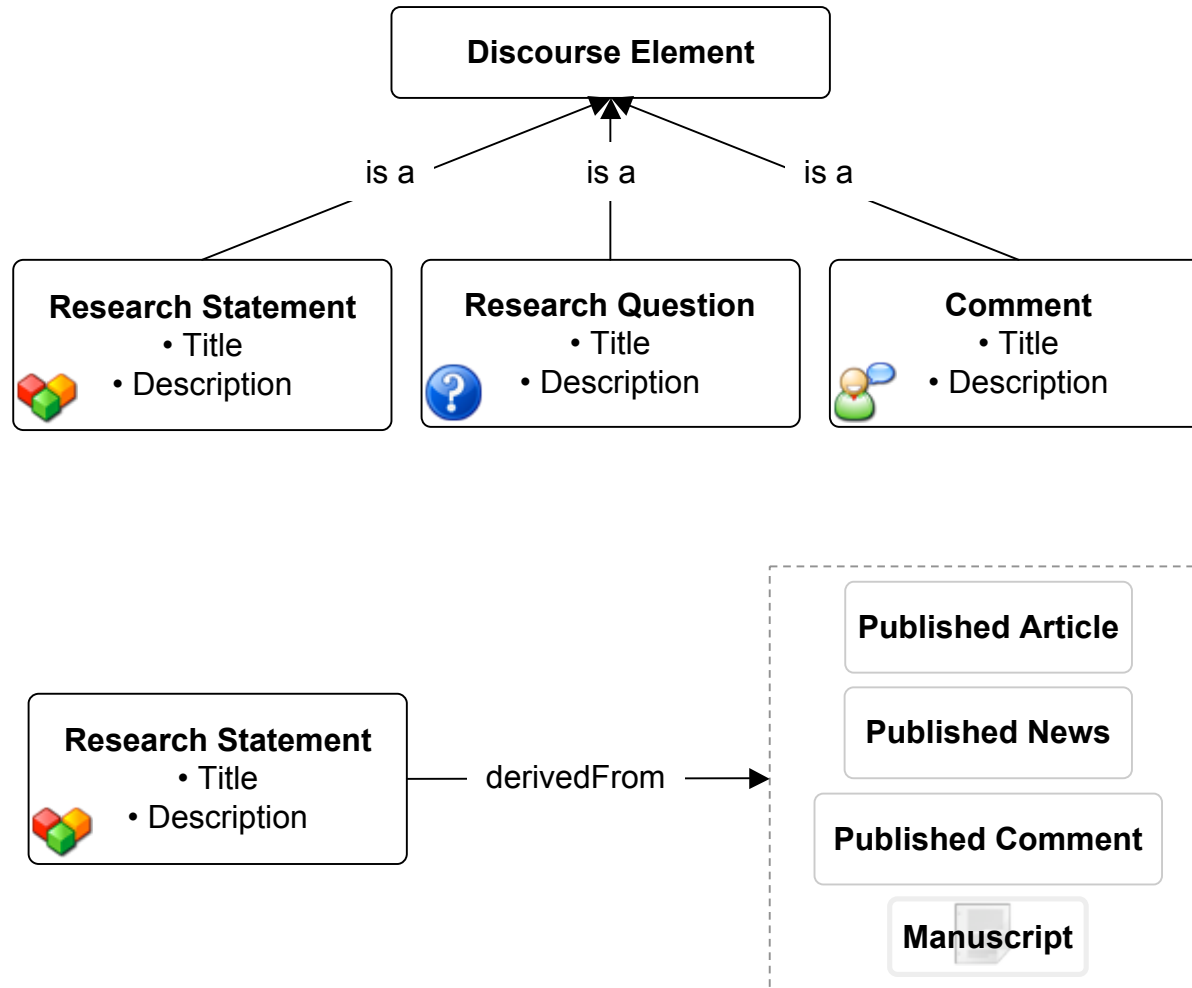
SWAN Deployment

- SWAN will be deployed on the Alzheimer Research Forum (Alzforum) website in 2007.
- Alzforum is a moderated, scientific web community, for the Alzheimer Disease (AD) research community, with over 4,000 registered members.
- A substantial proportion of the world's AD researchers are members of Alzforum.

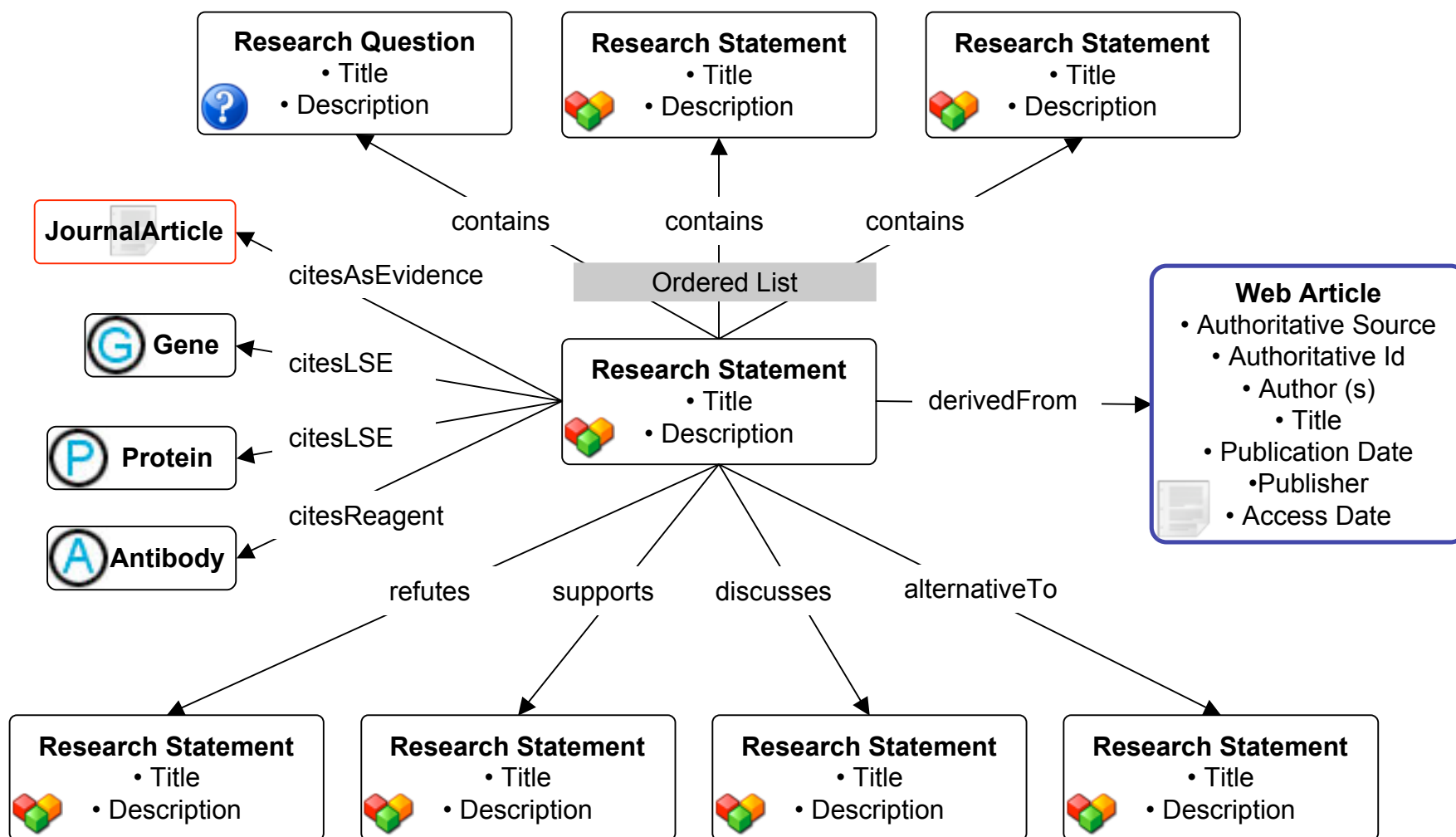
SWAN Main Hierarchy



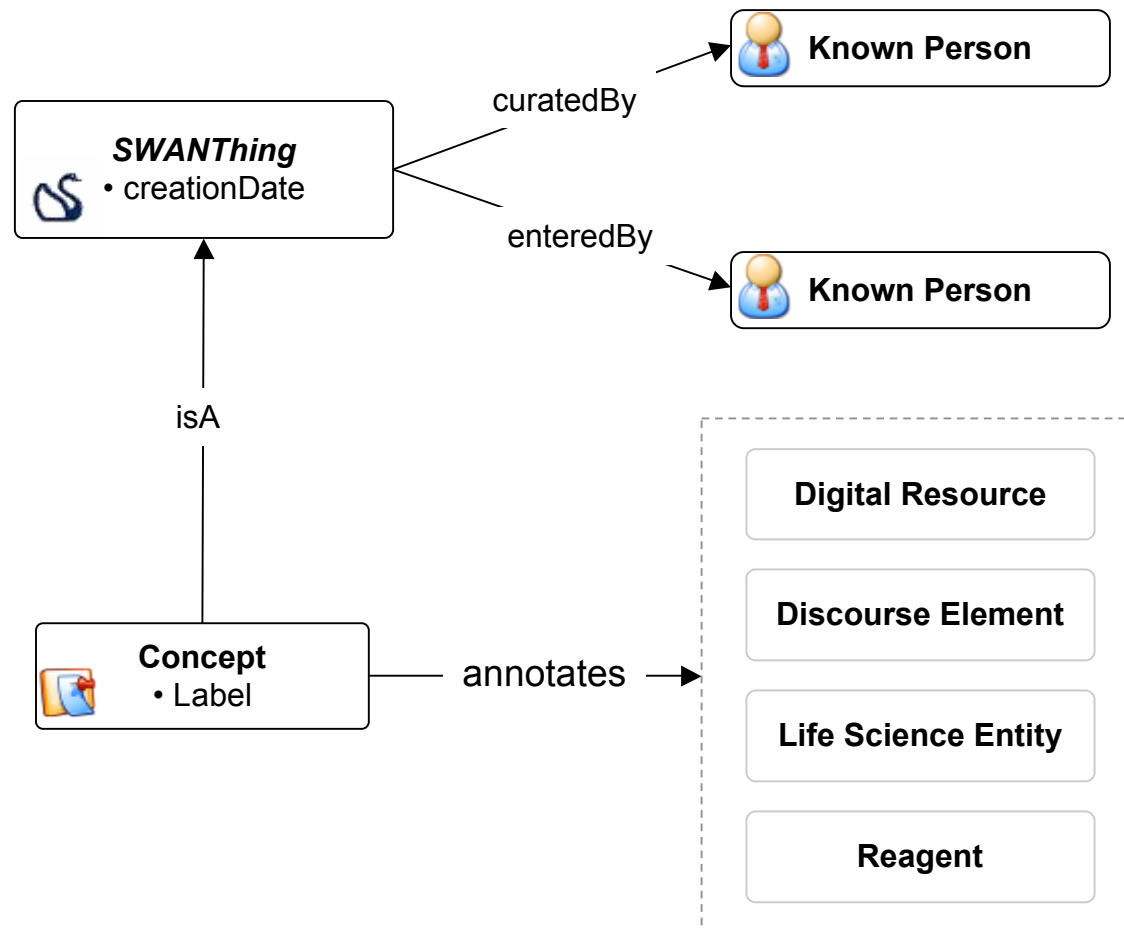
Discourse Elements



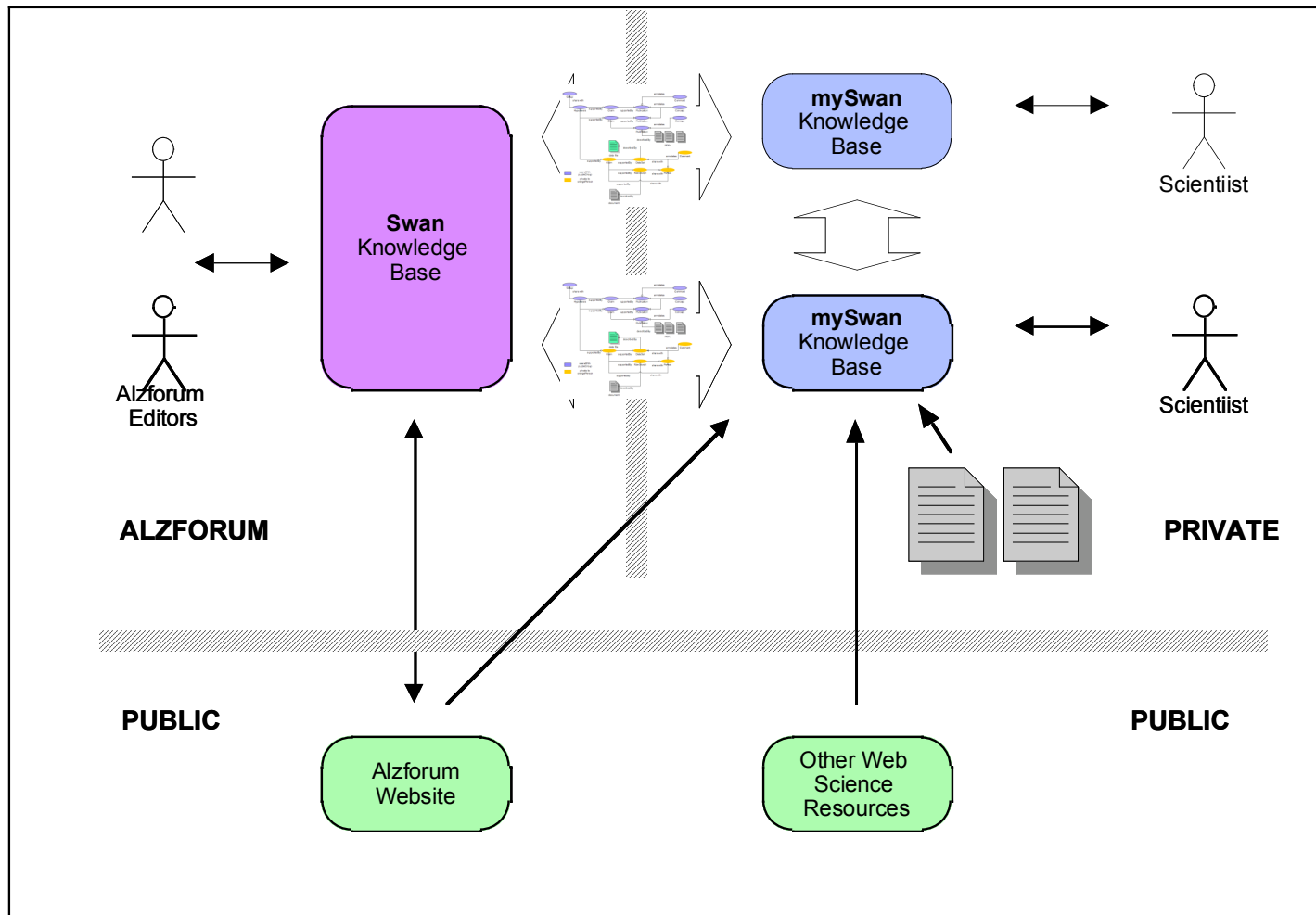
Research Statement



Concepts (Tags)



Community-Individual Interaction



Hypothesis Detail

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Hypothesis: Intramembranous A β dimer
Author: [V. Marchesi](#)
Abstract: Alzheimer's disease is a complex neurodegenerative process that is believed to be due to the accumulation of short, hydrophobic peptides derived from amyloid precursor proteins by proteolytic cleavage. It is widely believed that these A β peptides are secreted into the extracellular spaces of the CNS, where they assemble into toxic oligomers that kill neurons and eventually form deposits of senile plaques. This essay explores the possibility that a fraction of these A β peptides never leave the membrane lipid bilayer after they are generated, but instead exert their toxic effects by competing with and compromising the functions of intramembranous segments of membrane-bound proteins that serve many critical functions. Based on the presence of shared amino acid sequences containing GxxG motifs, I speculate that accumulations of intramembranous A β peptides might affect the functions of amyloid precursor protein itself and the assembly of the PS1, Aph1, Pen 2, Nicastrin complex.
Primary Citation: [Marchesi VT. An alternative interpretation of the amyloid A \$\beta\$ hypothesis with regard to the pathogenesis of Alzheimer's disease. Proc Natl Acad Sci U S A. 2005 Jun 28; 102\(26\):9093-8](#)
This hypothesis makes the following claims:
1. [A \$\beta\$ is first detected intraneuronally, not in extracellular spaces](#)
[Comments\(9\)](#) [Supportive Evidence\(1+7\)](#) [Alternative Research Statements\(1\)](#) [Genes\(3\)](#) [Grants \(2\)](#)
[Downstream Events/Genetics](#) [Downstream Events/Animal Models](#)

Research Statement - Example 1

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Research Statement SWAN-RS-1

[Comments](#) [Supportive Evidence](#) [Alternative Research Statements](#) [Genes](#) [Grants](#)

Title: A β is first detected intraneuronally, not in extracellular spaces

Abstract:
Transgenic mice expressing fAD APP either alone or in combination with fAD PS1 mutations and Tau exhibit amyloidogenesis, and other pathological features of AD but demonstrate variable extent of disease phenotypes such as neurological deficits, neuronal degeneration and learning defects. Interestingly, most immunologically detectable A β is first detected **intraneuronally**, not in **extracellular spaces**.

Author: [V. Marchesi](#)

Concepts: [Downstream Events/Genetics](#), [Downstream Events/Pathway](#)

Part of: [Intramembranous A \$\beta\$ dimer](#)

Claimed in: [Marchesi VT. An alternative interpretation of the amyloid Abeta hypothesis with regard to the pathogenesis of Alzheimer's disease. Proc Natl Acad Sci U S A. 2005 Jun 28 ; 102\(26\):9093-8](#)

Supported by:

- Journal Article:**
[Oddo et al., 2003](#)
- Comment:** [Koo, E:](#) extracellular A β , whether oligomers or aggregated fibrils, are insufficient to injure neurons...[more](#)
 - » [McGowan et al., 2005](#)
- Comment:** [Selkoe D:](#) Primary neurons cultured from Down syndrome brains observed robust

Linking Across Hypotheses

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7. A β 40 and 42 are enriched in sucrose gradient fractions of brain membrane fragments of Tg2576 mice, consistent with the notion that proteolytic cleavage of APP dimers results in accumulation of A β remaining embedded in the lipid bilayer.

[Comments\(2\)](#) [Supportive Evidence\(1\)](#)
[Downstream Events/Genetics/Pathways](#)
8. A β peptides do eventually accumulate extracellularly during disease progression, but the extracellular export of A β may be more complicated than simple release immediately following proteolytic cleavage.

[Comments\(0\)](#) [Supportive Evidence\(1\)](#)
[Downstream Events/Pathways](#)
9. Intramembranous A β peptides may alter the properties of neuronal cell membranes and may be toxic only if they remain within the lipid bilayer.

[Comments\(5\)](#) [Supportive Evidence \(0+7\)](#) [Alternative Research Statements\(1\)](#)
[Downstream Events/Pathways](#)
10. Inactive mutant forms of PS1 might result in APP cleavage product being left embedded in membrane.

[Comments\(0\)](#) [Supportive Evidence\(0\)](#)
[Downstream Events/Pathways](#)
11. The "channel hypothesis" proposes that extracellular A β can re-insert into the membrane, associate together and create channels that allow lethal levels of calcium into the cell.

[Comments\(2\)](#) [Supportive Evidence\(2\)](#)
[Downstream Events/Pathways](#)
12. Equally plausible is that A β peptides never leave the membrane

[Comments\(2\)](#) [Supportive Evidence\(2+4\)](#)
[Downstream Events/Pathways](#)
13. Persistence of A β dimers in the membrane over a long time could have significant impact on health of neurons, and could influence the behavior of receptors or channels.

[Comments\(9\)](#) [Supportive Evidence \(0+8\)](#)
[Progression/Pathway](#)
14. Concept of dimeric A β persisting in membranes differs from widely held view that A β is released into extracellular space to form oligomers and fibrils.

A Conflicting Statement

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- » [Neve et al., 2000](#)
- » [Fukuchi et al., 1992](#)
- Comment:** [Koo, E.](#) Work from Fred Van Leuven's and Jie Shen's laboratories has shown...[more](#)
- » [Dewachter et al., 2002](#)
- » [Saura et al., 2005](#)
- Comment:** [Dewachter & Van Leuven](#): From our view, a most interesting point of Dr. Marchesi's hypothesis is...[more](#)
- » [Dewachter et al., 2002](#)
- Comment:** [Dewachter & Van Leuven](#): Completely in line with our findings, data published earlier this year...[more](#)
- » [Saura et al., 2005](#)
- » [Herms et al., 2002](#)
- » [Ris et al., 2003](#)

Alternative:

- Comment:** [Dewachter & Van Leuven](#): Evidence in ADAM10-deficient mice convincingly...[more](#)

Conflicting Research Statements:

- Research Statement:** [Aβ⁵⁶ hypothesis RS-7](#): Extracellular-enriched dodecameric 56 kDa assemblies and less abundant nonameric 40 kDa assemblies appear at 6 months of age with considerable variability between animals of the same age, and remain stable between ages 6 to 13 months. This satisfies one of the criteria for Aβ*. No other Aβ assemblies were found that cause the second stage of memory loss that occurs between 12–15 months age.

Related to:

- **Genes:** [APP](#), [PS1](#), [Tau](#)

Navigating to Conflicting Hypothesis

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Title: Extracellular-enriched dodecameric 56 kDa assemblies satisfies one of the criteria for A β *.



Abstract:
"As the 56-kDa and 40-kDa species appeared at 6 months of age and remained stable between the ages of 6 and 13 months, they fulfilled the criteria for being designated as A β * and thus represented viable candidates for A β assemblies that cause memory deficits. We found no further increase in A β assemblies in old mice to correspond to the second drop in memory function at 15 months?. ?We found no intracellular or membrane-associated A β species or CTFs correlating with the onset of memory deficits in 6-month-old Tg2576 mice."



Author: [K. Hsiao-Ashe](#)

Concepts: [Downstream Events/Genetics](#), [Downstream Events/Animal Models](#)

Part of: [A \$\beta\$ *56 hypothesis](#)

Claimed in: [Lesné S, Koh MT, Kotilinek L, Kaye R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. Nature. 2006 Mar 16; 440\(7082\):352-7.](#)

Supported by:
 **Figures:** [Figures 1c, 3g, 3h; Supplementary Figures 3 and 4a;](#)
 **Comment:** [Le Vine, H:](#) The importance of these observations is that they direct attention to extracellular events as being important in the maturation of trimers and tetramers into A β *56. This has not previously...[more](#)

Alternative:
 **Comment:** [Dewachter & Van Leuven:](#) Evidence in ADAM10-deficient mice convincingly...
[more](#)
 **Comment:** [Wolfe, D:](#) "Going forward it will be critically important to validate the human

Conflicting Hypothesis

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 ☐ Comment [120]
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Hypothesis: A β *56 hypothesis
Author: [Karen Hsaio Ashe](#) and colleagues
Abstract: Alzheimer's disease is a complex neurodegenerative process that is believed to be due to the accumulation of short, hydrophobic peptides derived from amyloid precursor proteins by proteolytic cleavage. It is widely believed that these A β peptides are secreted into the extracellular spaces of the CNS, where they assemble into toxic oligomers that kill neurons and eventually form deposits of senile plaques. This essay explores the possibility that a fraction of these A β peptides never leave the membrane lipid bilayer after they are generated, but instead exert their toxic effects by competing with and compromising the functions of intramembranous segments of membrane-bound proteins that serve many critical functions. Based on the presence of shared amino acid sequences containing GxxG motifs, I speculate that accumulations of intramembranous A β peptides might affect the functions of amyloid precursor protein itself and the assembly of the PS1, Aph1, Pen 2, Nicastrin complex.
Primary Citation: [Lesné S, Koh MT, Kotilinek L, Kaye R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. Nature. 2006 Mar 16; 440\(7082\):352-7](#)
This hypothesis makes the following claims:

- Tg2576 mice, a good pre-clinical model of AD, exhibits the earliest memory function decline at 6 months age, preceding neuropathology**
[Comments \(5\)](#) [Supportive Evidence\(6\)](#) [Alternative Research Statements\(1\)](#) [Grants \(2+\)](#)
[Progression/Pathways](#) [Progression/Animal Models](#)
- Early cognitive decline followed by a period of stabilization in Tg2576 does not correspond to rapidly increasing amounts of A β**
[Comments \(0\)](#) [Supportive Evidence\(4\)](#) [Alternative Research Statements\(0\)](#) [Grants \(2\)](#)
[Progression/Pathways](#) [Progression/Animal Models](#)

Comparing Hypotheses with Pathogenic Narratives

Title	Initial Conditions	Perturbations	Downstream Events	Progression	Convergence	Therapy
Intraneuronal A β dimers (Marchesi 2005)	APP, PS1, GPA, ErbB,		Intramembranous A β 40 and A β 42, APP dimers,	Channels of A β 40 allow lethal Ca ²⁺ into cells,	Intramembranous A β dimers reduces receptor function,	Therapies directed to extracellular A β may miss toxic species,
A β *56 (Lesne et al, 2006)	APP, PS1 bram,		Soluble A β assemblies disrupt memory.		Tg2576 exhibit early memory decline preceding neuropathology,, A β *56 can cause memory deficit in healthy rats	Therapies to A β *56 may provide reversibility in disease prior to permanent damage,
Ceramide and aging (Costantini et al, 2005)		Late onset AD associated with aging, hypercholesterolemia, atherosclerosis, head trauma, stroke. Ceramide involved in neurodegeneration.	Smase generates ceramide,, nSMadse2 regulated by p75 neurotrophin receptor	Chronic increase in intracellular ceramide inhibits axonal elongation and activates cell death.		
Cholesterol and aging (Costantini et al, 2005)		High concentration of cholesterol in brain or cells can increase A β	A β oxidizes membrane cholesterol, liberates H ₂ O ₂ and increases oxidative stress	Aging is associated with progressive oxidation of circulating lipoprotein, leads intracellular accumulation in lysosomes		Statins
Pathways of A β oligomerization (Bitan et al., 2003)			Photocrosslinking reveals A β 42 Pentamers and hexamers as basic units for further assembly		Oligomers of Ab42 assemble into paranuclei which leads to fibrillar structures. Ab40 lacks ability to form paranuclei	

SWAN relationships & interactions with other projects

- Alzheimer Research Forum
- Massachusetts ADRC
- W3C HCLS WWW2007 Demo
- IBM SLRP (Boca)
- SenseLab (Yale) - under discussion
- HyBrow (Stanford) - under discussion
- IIC - Stem Cell Digital Collaboration Framework (Harvard) - under discussion

The SWAN Team

- Harvard/MGH: Marco Ocana, Paolo Ciccarese, Tim Clark
www.mindinformatics.org
- Alzforum: Elizabeth Wu, Gwen Wong, June Kinoshita
www.alzforum.org
- IBM: Ben Szekley
- Thanks to: Anne Young, Brad Hyman, Zane Hollingsworth, Marian DiFiglia & Dora Kovacs - MGH; Dean Hartley - BWH; Andy Seaborne & Steve Cayzer - HP Labs, Bristol, UK; Sean Martin - IBM Advanced Technology Group.

website: <http://swan.mindinformatics.org>



The Beautiful Swan – by [William Nicholson](#), British (1872–1948), color lithograph after a woodcut, 1900. Campbell 73b.